# Discussion of EPA's use of Dose Addition for Mixtures Risk Assessment: Current and Future Applications

Authors: Glenn Rice, Linda Teuschler, Richard Hertzberg, Jason Lambert, Marian Olsen, Rita Schoeny, Jane Ellen Simmons, Jeff Swartout

Meeting of the Risk Assessment Forum (RAF)
Cumulative Risk Assessment (CRA) Technical Panel
September 29, 2016

# Document History

- 2010 EPA's Human Health Risk Assessment Colloquium recommends Risk Assessment Forum (RAF) respond to NRC's 2008 Phthalates Report[1]
  - NRC Report includes critiques of approaches that assume dose addition for chemical mixtures and are used by EPA
- 2011 RAF Cumulative Risk Assessment (CRA) Panel Tri-Chairs initially consider developing report on dose addition (DA) practices in EPA
  - Tri-Chairs when project initiated: Linda Teuschler, Gino Scarano, Chuck Maurice
  - Current chair: Wendy O'Brien
- Document arose from EPA's interest in advancing CRA
- RAF CRA Technical Panel Working Group on Additivity Empaneled
  - First co-leads: Linda Teuschler (retired) and Rita Schoeny (retired)

[1]National Research Council's (2008) Phthalates and Cumulative Risk Assessment: The Tasks Ahead

# Need for the Document

1) Issues recognized during applications of DA methods in human health risk assessments of environmental chemical mixtures

2) Publication of new/enhanced risk assessment methods based on DA

3) Scientific advances that increase understanding of responses to chemicals at multiple levels of biological organization

- Toxicology
- Cell biology
- Biochemistry
- Bioinformatics

# Document Purpose

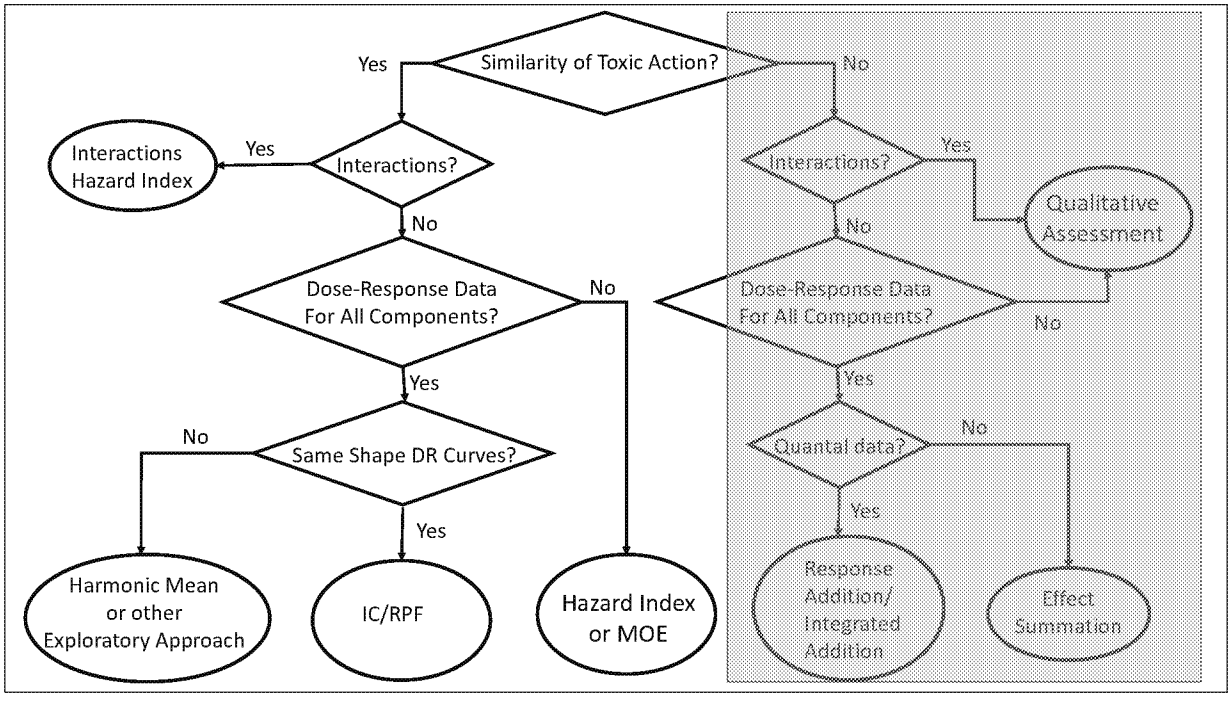
- Elucidate and update information on EPA's use of DA approaches in chemical mixture risk assessments
- Discuss EPA's theoretical basis for and current, practical applications of DA approaches in chemical mixtures risk assessment
- Considering new sources of toxicological data including high throughput (HTP) platforms, discuss possible future roles of DA approaches
  - Toxicogenomics ("-omics")
  - Chemoinformatics (e.g., structure activity relationships, read across)
  - Bioinformatics
  - Cell-based bioactivity screening assays (e.g., receptor-ligand binding).

# Document Organization: 6 Chapters and Appendix

- Chapter 1 Introduction
- Chapter 2 Additivity concepts and DA approaches presented in EPA-wide documents (i.e., guidelines and guidance)
- Chapter 3 DA approaches developed by EPA Program Offices or ORD
- Chapter 4 Criteria for grouping chemicals for DA methods

## Document Organization: Chapter 5
## Issues Concerning Similarity of Dose Response Curves, Dose Additivity and Choice of Model for Estimating Mixture Response

1. Present empirical and biological concepts that support DA methods
   - Examine key events in adverse outcome pathways (AOP)
   - Establish similarity of toxic action
   - Evaluate similarity among shapes of dose-response curves for DA chemicals
     - Different curve shape does not exclude use of dose addition methods
2. Using mathematical functions in EPA's BMDS to determine curve shape
   - Methods for evaluation of similarity of shape in Appendix A
3. Approaches when DA component curve shapes are similar (constant relative potency)
4. Exploratory approaches when DA component curves are not similar (dose-dependent relative potency)
5. Decision tree for selecting among component mixture methods


Similarity of Toxic Action?
Yes
No
Interactions?
Yes
Interactions Hazard Index
No
Dose-Response Data For All Components?
No
Yes
Same Shape DR Curves?
No
Yes
Harmonic Mean or other Exploratory Approach
IC/RPF
Hazard Index or MOE
Interactions?
Yes
Qualitative Assessment
No
Dose-Response Data For All Components?
No
Yes
Quantal data?
No
Yes
Response Addition/ Integrated Addition
Effect Summation

## Document Organization: Chapter 6

1. Potential future uses of data generated through HTP toxicity methods in mixture risk assessment methods based on DA
2. Elucidation of toxicodynamics events for DA

## Document Organization: Appendix A

1. Approaches that test for lack of similar dose-response curve shape (lack of constant relative potency)
2. Discussion of predicting mixture responses when the shapes of the dose-response curves differ

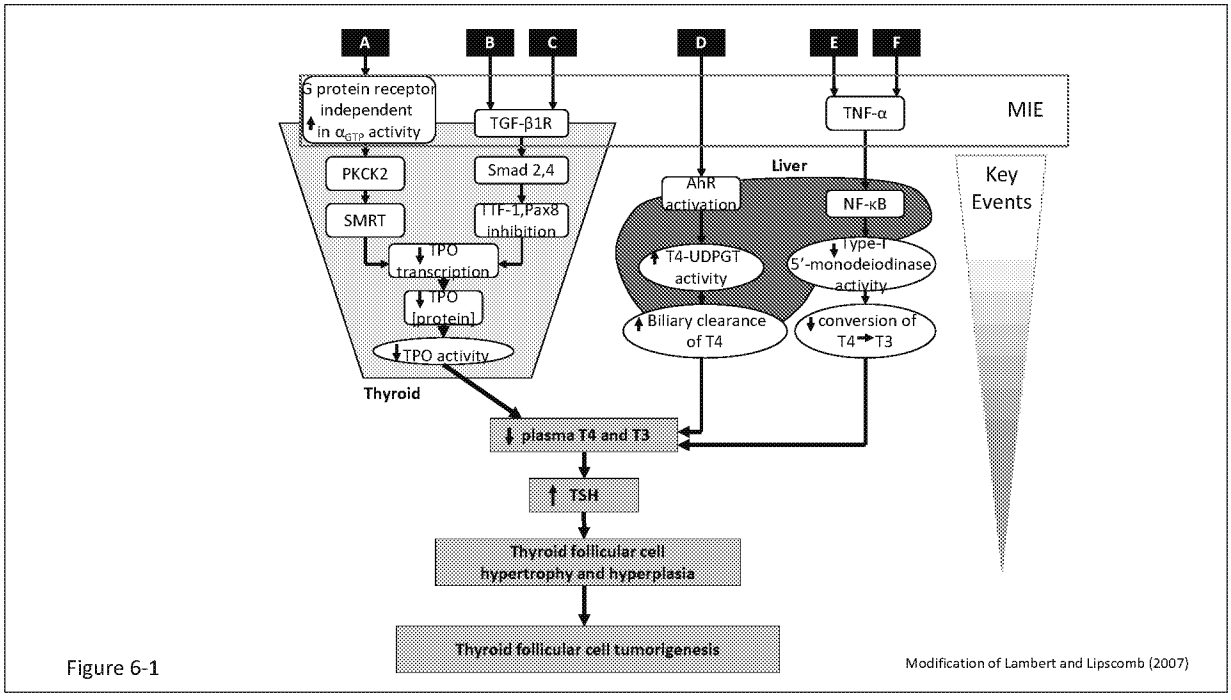



Figure 6-1

Figure 6-1: PKCK2 = protein kinase casein kinase 2; SMRT = silencing mediator of retinoic acid and thyroid hormone receptor; TPO = thyroid peroxidase; TGF-β1R = transforming growth factor-beta1 receptor; Smad 2,4 = mothers against decapentaplegic homolog 2 and 4; TTF-1 = thyroid transcription factor-1; AhR = aryl hydrocarcbon receptor; UDGPT = UDP glucuronosyltransferase; TNF-α = tumor necrosis factor-alpha; NF-κB = nuclear factor kappa B; T4 = thyroxine; T3 = triiodothyronine; TSH = thyroid stimulating hormone; MIE = molecular initiating event

# Differences from 2014 Version

- Limited the discussion of other additivity methods (not DA)
- Removed: *similarity of toxic action* as term encompassing mode and mechanism of action
- No "endorsements": text removed giving appearance of guidelines-like recommendations or endorsement of specific methods
- Replaces screening strategies for hazard index and response addition
  - Broadly describes a stepwise approach for excluding chemicals from analyses
- No discussion of mixtures uncertainty factors
- No discussion of assigning EDx levels for RPFs

# Many improvements over the 2014 version

- Document streamlined and re-organized
- Improved presentation of toxicodynamics and its role in deciding to use DA
- Added decision tree –considers toxicological and dose-response information to inform choice of DA method; easily implemented
- Improved descriptions of DA methods and clarification of source of methods: EPA guideline/guidance; ORD/Program Office; Outside EPA
- Updated criteria for grouping chemicals for DA approaches
- Expanded and improved discussion of the state of the science of methods for examining shape of dose-response curves
- Characterized potential uses of HTP data

# Thanks!

| | |
|---|---|
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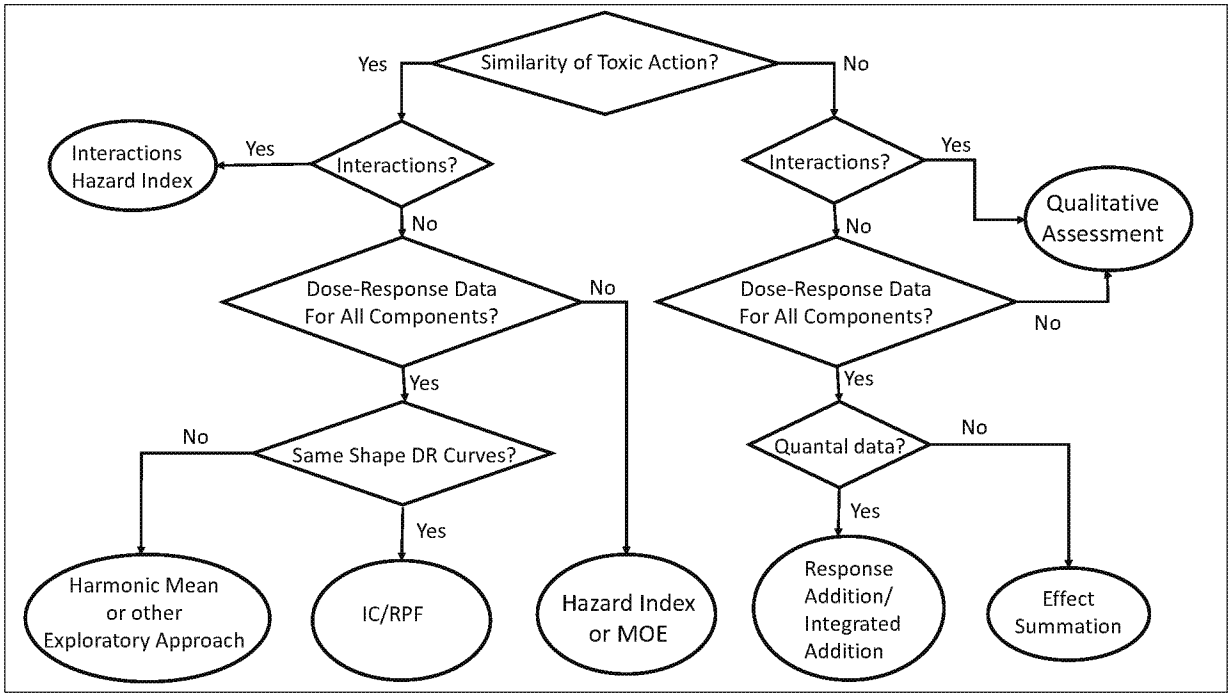
# Supplemental Materials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| Major Review Comments on 2014 Version | Response |
|---|---|
| Confusing document organization | Document streamlined; major structural re-organization articulated in Chapter 1 |
| Improve organization of introductory materials Increase clarity of document's purpose | Revised Foreword and Chapter 1: Document Purpose, Background, and General Consideration when using DA methods in risk assessment |
| Focus on Dose Additive Methods | Limit discussion of other additivity methods; context for dose additive methods |
| Describe uncertainty/confidence in each approach | Additional discussion of strengths and limitations of various dose-additive approaches included throughout the document |
| Improve discussion of regulatory context of different approaches; Distinguish EPA-wide dose-additive methods from those of individual Program Offices | Document revised: EPA-wide dose-additive methods described in Chapter 2; other EPA dose-additive methods including those responsive to regulations discussed in Chapter 3 |
| Do not endorse methods in this document | No "endorsements" are presented: text removed giving appearance of guidelines-like recommendations or endorsement of specific methods (other than those endorsed in program-specific guidance) |
| Improve "handling" of NAS phthalates report and other NAS reports | All the relevant NAS reports were placed into the context of other comprehensive methodology reports addressing dose additivity |
| Do not develop a new term encompassing mode and mechanism of action. Increase focus on Adverse Outcome Pathway (AOP). | Replaced *similarity of toxic action* as term encompassing mode and mechanism of action with tiered understanding of AOPs and key events. Document summarizes transition in toxicology to AOP that is occurring, particularly in Chapter 6 |
| Concerns over screening strategies proposed | Replaced screening strategies for hazard index and response addition with description of general stepwise approach for excluding chemicals from analyses using dose-additive methods |
| Do not discuss mixtures uncertainty factors | Removed discussion of mixtures uncertainty factors |
| Do not discuss assigning EDx levels for RPFs | Removed discussion of assigning EDx levels for RPFs |
| Applicability of dose-additive methods to different lifestages, populations, and genders. | Statement added in Chapter 1: "Unless otherwise noted, the mathematical models described ... should be considered applicable to human health risk assessments and ecological risk assessments. Further, ... these models should be considered applicable to all stages of life, potentially including (but not limited to) both prenatal and postnatal lifestages (e.g., from birth, through infancy, adolescence and adulthood), as well as pregnant, nursing, and elderly populations." |
| Improve clarity of presentation on applying dose-additive methods when dose-response curves are not the same shape, resulting in non-constant relative potency. | Chapter 5 (developments in dose addition methods) substantially rewritten to provide more detail. Section added on using exploratory methods when relative potencies are not constant. Also added flowchart describing the choice of addition methods for specific data scenarios. Examples added in Appendix A. |